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#3

NIDN-10394

Application of: O. Homestad Group Art Unit: To be assigned
Serial Number: 09/923,074 Examiner: To be assigned
Filing Date: August 6, 2001
Title: Preparation of Iodixanol

COMPLETION OF CLAIM FOR PRIORITY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby submit the official certified copy of the priority document number **GB 9903109.8** in connection with the above identified application, benefit of which is claimed in the declaration of this application. The Examiner is most respectfully requested to acknowledge receipt of this certified copy in the next Official Office Action.

Respectfully submitted,

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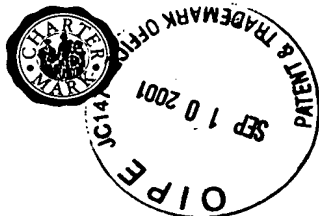


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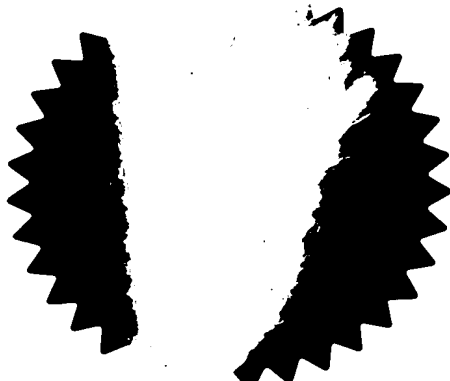
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2. Patent application number (The Patent Office will fill in this part)	9903109.8		
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4. Title of the invention	Process 20/8/91 Form 5/77		
5. Name of your agent (if you have one)	Frank B. Dehn & Co. A B Rollins et al 179 Queen Victoria Street London EC4V 4EL Amersham plc Amersham Laboratory White Lion Road Amersham HP7 9LL		
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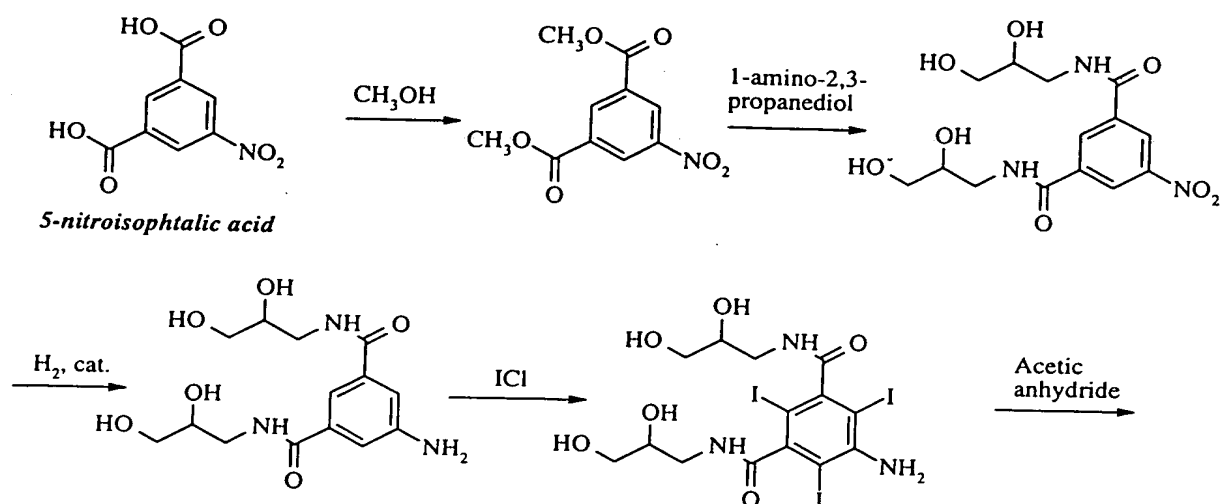
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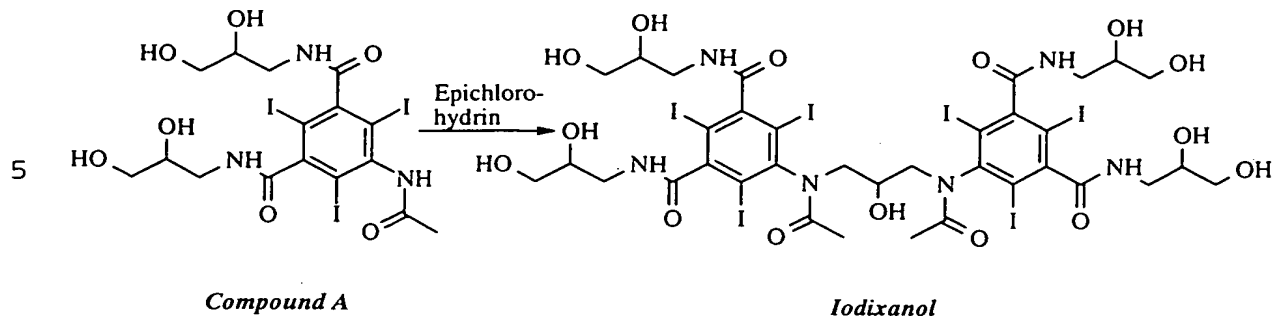
PROCESS

This invention is concerned with the synthesis of
5 iodixanol.

Iodixanol (1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-
dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-
hydroxypropane) is a non-ionic X-ray contrast agent
10 which is currently manufactured in large quantities. A
number of methods are known for its preparation but
these are all multistep processes and the cost of the
final formulated product thus mainly depends on these
processes. It is therefore important to optimise these
15 processes for both economic and environmental reasons.

Three main processes are known for the preparation of
iodixanol, all of which start with 5-nitroisophthalic
acid. In the first process (NO 161358), the following
20 route is used, via the final intermediate 5-acetamido-
N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-
isophthalamide ("Compound A"):





10 The problem with this process is that a yield of only
 18% is reported in the given example, and the product is
 purified by preparative chromatography. When we have
 repeated the example, we have found that the low yield
 is due to incomplete conversion of Compound A to
 15 iodixanol. After 40-60% of the starting material is
 consumed, over-alkylation of iodixanol starts to
 dominate over the desired reaction, causing the net
 content of iodixanol in the reaction mixture to
 decrease. In fact, 40-60% conversion to iodixanol seems
 20 to be the maximum obtainable. Due to this low
 conversion, common crystallisation techniques are not
 able to purify the product to the necessary level, and
 preparative liquid chromatography is the only way to
 obtain a pure product. The combination of low yields
 25 with an expensive purification method such as
 preparative chromatography is a serious disadvantage in
 an industrial process.

Priebe et.al. (*Acta Radiol.* 36 (1995), Suppl. 399, 21-
 30 31) describe another route which avoids the difficult
 last step of the above process. However, the route
 involves eight reaction steps from 5-nitroisophthalic
 acid, which is undesirable, and one of the steps
 includes chlorination with thionyl chloride, which is
 35 extremely corrosive. Also, the introduction of the
 iodine atoms takes place very early in the sequence,
 which is disadvantageous as iodine is the most expensive

reagent in the process. The yield and final purification method for this route have not been reported.

5 The third route to iodixanol involves the synthesis of 5-amino-2,4,6-triiodoisophthalic acid (WO 96/37458) and then its dichloride (WO 96/37459), followed by conversion into Compound A (US 5705692) and finally dimerisation as in the first process above. This method
10 thus has the same disadvantages as the first, and also uses an undesirable acid chlorination step.

We have now surprisingly found that unreacted Compound A from one dimerisation batch, as produced for example in
15 the first and third processes described above, can be recovered from the reaction mixture by a very simple process, and reused in a later batch. This increases the net yield from successive batches on an industrial scale dramatically. Additionally, the removal of most
20 of the unreacted Compound A from the reaction mixture allows the expensive preparative liquid chromatography purification to be replaced by conventional crystallisation methods, still providing iodixanol suitable for pharmaceutical use.

25 The invention thus provides a process for the preparation of iodixanol by dimerisation of Compound A in which, after the dimerisation step, unreacted Compound A is precipitated from the reaction mixture and
30 recovered for re-use.

The dimerisation step itself may be carried out as described in NO 161368 and WO 98/23296, for example using epichlorohydrin, 1,3-dichloro-2-hydroxypropane or
35 1,3-dibromo-2-hydroxypropane as the dimerisation agent. The reaction is usually carried out in a non-aqueous solvent, preferably 2-methoxyethanol or methanol, and

generally results in the conversion of 40-60% of Compound A to iodixanol. Dimerisation in pure water or mixtures of water and one or more alcohols (e.g. C₁₋₆-alkanols) is also possible.

5

Precipitation of Compound A from a non-aqueous reaction mixture can be effected after addition of water, for example in an amount of 1-2, preferably 1.3-1.8 L/kg Compound A used as starting material. If water is present in the reaction mixture, the amount of water added for precipitation can be reduced accordingly. An alcoholic co-solvent (e.g. a C₁₋₆ alkanol such as methanol) may additionally be used, for example in an amount of 0.5-2, preferably 0.8-1.5 L/kg Compound A used as starting material. In some instances, traces of undissolved material remain after the addition of water and alcohol and these can be dissolved by addition of alkali, e.g. sodium hydroxide. The pH of the solution is then adjusted to about 10-11 by addition of an acid, e.g. hydrochloric acid, to provoke precipitation of unreacted Compound A and if necessary the temperature can be adjusted to 15-40°C, preferably 18-30°C. The solution is optionally seeded with crystals of Compound A to initiate the precipitation of Compound A, while the iodixanol formed stays in solution.

Further addition of acid to a pH of 2-5, preferably 3-4, can increase the yield of the recovery process by increasing the supersaturation of non-ionic Compound A. After this final pH adjustment, the suspension is advantageously stirred for some hours to enhance the precipitation of Compound A, e.g. 4-30 hours, preferably 8-20 hours. The precipitate should then be separated from the reaction mixture by a conventional technique, such as centrifugation or filtration, and optionally washed with a suitable solvent, e.g. water or methanol.

The filtrate from the separation mainly contains iodixanol and small fractions of related iodinated aromatic compounds, in addition to salts and remaining epichlorohydrin and derivatives thereof. This mixture
5 can be purified by conventional desalination and crystallisation methods to obtain iodixanol suitable for pharmaceutical use. Chromatographic purification of the crude iodixanol in the filtrate is not necessary.

10 The separated Compound A from the recovery process can optionally be recrystallised, for example from water/methanol or another alkanol. Thus, the moist material from the filtration/centrifugation may be dissolved in water in the presence of alkali. The
15 amount of water should be about 2-7 l/kg of Compound A, preferably 3-5 l/kg. Alkali, e.g. aqueous sodium hydroxide, should be added until all traces of undissolved material are removed. The solution may optionally be filtered to remove remaining traces of
20 undissolved matter. An alcohol, e.g. methanol (0.5-1.5 l/kg of Compound A, preferably 0.5-1.0 litres/kg) may then be added, and the mixture heated to 40-80°C, preferably 50-60°C. Adjustment of pH by an acid, e.g. hydrochloric acid, causes pure Compound A to
25 precipitate. The mixture may optionally be seeded with a small amount of Compound A crystals. Maximum yield from the recrystallisation is obtained if the pH is finally adjusted to about 5-7, e.g. with hydrochloric acid, followed by cooling to 10-25°C. The slurry may
30 optionally be stirred at this temperature to enhance the crystallisation, e.g. 2-18 hours. The precipitate is separated from the suspension by any conventional technique, for instance centrifugation or filtration, and optionally washed with water, methanol or another
35 suitable alkanol. The recovered Compound A may advantageously be dried, e.g. under reduced pressure, before reuse in a new dimerisation.

Recovered and fresh Compound A may in any ratio be mixed and used in a new dimerisation reaction as described above, including subsequent recovery of unreacted substrate.

5

The following examples illustrate the invention.

EXAMPLE 1

10 Compound A (366 g) was dissolved in a solution of NaOH(23 g) in 2-methoxyethanol (360 ml) at 50°C. The temperature was decreased to 15°C when all solids were dissolved, and conc. HCl (28 g) was added to the solution. Epichlorohydrin (13 g) was added in one
15 portion, and the reaction was monitored by HPLC. After 46 hours the content of iodixanol in the reaction mixture was 49.6%. Water (575 ml) was added, and the temperature was increased to 19°C. The solution was at this time clear, so no further addition of sodium
20 hydroxide was necessary. The pH was adjusted to 10.8 by 18% hydrochloric acid, and the solution seeded with 1 g of Compound A. The pH of the resulting suspension was further pH-adjusted with 18% hydrochloric acid to pH 4.0. The suspension was left with stirring overnight
25 before filtration and washing with water (60 ml) on the filter. The filtrate was further desalinated and crystallised by conventional methods, providing iodixanol suitable for pharmaceutical use. The material on the filter was analysed on HPLC, showing 94.3%
30 Compound A and 5.1% iodixanol.

EXAMPLE 2

The recovered Compound A from Example 1 was taken
35 directly from the filter without drying, and completely dissolved in water (440 ml) and 50% NaOH(aq) (15 ml). The solution was filtered through a 3 µm filter to

remove traces of insoluble matter, and some more water (50 ml) was added to the filtrate. Methanol (95 ml) was added to the solution, and the temperature was increased to 60°C. The pH was reduced from 11.5 to 9.8 with 18% hydrochloric acid, and 0.8 g seeds of Compound A was added. After 30 minutes, the pH was further reduced to 6 with 18% hydrochloric acid. The temperature was gradually reduced to 15°C, and the precipitated material was filtered, washed with methanol (140 ml) and dried under vacuum at 60°C. The yield of pure Compound A (> 99% by HPLC) was 118 g, corresponding to 32% of the starting material in Example 1.

The recovered Compound A (118 g) was combined with fresh Compound A (248 g) in a new dimerisation similar to Example 1, giving nearly identical results as in Example 1.

Claims

1. A process for the preparation of iodixanol by dimerisation of 5-acetamido-N,N'-bis(2,3-
5 dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("Compound A") in which, after the dimerisation step, unreacted Compound A is precipitated from the reaction mixture and recovered for re-use.
- 10 2. A process according to claim 1 in which the dimerisation step is carried out using epichlorohydrin, 1,3-dichloro-2-hydroxypropane or 1,3-dibromo-2-hydroxypropane as the dimerisation agent in a non-
15 aqueous solvent or in water or a mixture of water and one or more alcohols.
3. A process according to claim 2 in which the dimerisation agent is epichlorohydrin and the solvent is 2-methoxyethanol or methanol.
20
4. A process according to any preceding claim in which precipitation of Compound A is effected with water, optionally together with an alcoholic co-solvent.
- 25 5. A process according to claim 4 in which the pH of the mixture is adjusted to 10-11 with acid to provoke precipitation, the temperature adjusted if necessary to 15-40°C and the solution optionally seeded with crystals of Compound A.
30
6. A process according to claim 5 in which further acid is added to a pH of 2-5.
7. A process according to any preceding claim in which
35 the Compound A recovered is recrystallised.

8. A process according to claim 1 in which, after separation of Compound A, the iodixanol-containing mixture is purified without the use of chromatographic methods.

ABSTRACT

5

PROCESS

10 A process for the preparation of iodixanol by
dimerisation of 5-acetamido-N,N'-bis(2,3-
dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("Compound
A") in which, after the dimerisation step, unreacted
Compound A is precipitated from the reaction mixture and
recovered for re-use. The process substantially
increases the net yield of iodixanol and simplifies its
purification.

15